

QUALITY BY DESIGN DRIVEN FORMULATION DEVELOPMENT AND OPTIMIZATION OF POOR SOLUBLE ANTI-HYPERTENSIVE DRUG FOR IMPROVED SOLUBILITY

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ABSTRACT

Objective: The objective of this study was to develop a polymeric composite of the poorly soluble antihypertensive drug felodipine with help of PVP K-30 and PEG 6000, using a Quality by Design (QbD) approach to enhance its solubility and, consequently, its bioavailability.

Methods: In this work, the quality target product profile (QTPP) was defined and Critical Quality Attributes (CQAs) were identified. Additionally, risk assessment analyses were carried out using the Ishikawa fishbone diagram to identify the Critical Material Attributes (CMAs) and/or Critical Process Parameters (CPPs) associated with the development of polymeric composite that could influence the Critical Quality Attributes (CQAs) of the drug product. The solubility of felodipine hydrochloride was improved by creating various polymeric composites with various concentrations of Poly Vinyl Pyrrolidone K30 (PVP-K 30) and Poly Ethylene Glycol 600 (PEG 600) by solvent evaporation method as Critical material attribute (CMA) as identified by risk assessment study and the CQAs viz drug solubility, drug content and drug release. These composites were designed using a 3² Face Central composite Design (FCCD) with a face-centered approach implemented in Design Expert software.

Results: After defining QTPP and CQA, risk assessment analysis was successfully used to identify CMA as well as CPPs. A total of thirteen PVP-PEG polymeric composites were developed and evaluated for FTIR spectra, Differential Scanning Colorimetry (DSC), X-Ray diffraction (XRD), and Scanning electron Microscopy (SEM). Data optimization was performed using response surface methodology, including contour and overlay plots. Solubility, drug content, and drug release of the optimized batch were found to be 21.55 mg/ml, 100%, and 78.314%, respectively. Three Validation Check batches (VC1-VC3) were developed and validated. Percent error for solubility ranges between-0.0019 to 0.0061, drug content ranges between 0.0005 to 0.0031 and solubility ranges between 0.0005 to 0.0011 that were very close to the predicted value, hence verifying the optimized data. Thus, by carefully using the QbD technique, the solubility of felodipine was enhanced by the effective development of a PVP-PEG polymeric composite.

Conclusion: The QbD approach was to be an effective tool to develop an optimized polymeric composite of PVP 30K and PEG 6000 of felodipine with improved solubility without exhaustive research.

Keywords: Central composite design, Characterization, Felodipine, PEG 6000, polymeric composite, PVP-K30

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INTRODUCTION

Improving the solubility of drugs and oral bioavailability is one of the critical challenges for drug development research, especially concerning oral drug delivery systems. Multiple strategies have been devised that can be classified broadly into physical and chemical modification of drug substances and alternative approaches. Physical modification techniques include the following: micronization, nanosuspension, polymorphism, amorphous forms, and co-crystallization along with dispersion within carriers like cryogenic processes, solid dispersions, eutectic mixtures as well as solid solutions [1].

A scientifically validated, Quality by Design (QbD) strategy helps to understand and manage the relationship between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), which are important for the Quality Target Product Profile (QTPP) [2]. CQAs, which include solubility, drug loading, and drug release of the developed polymeric composite, are caused by critical material parameters (CMPs) and critical process parameters (CPPs), such as the physicochemical properties of the felodipine, the type and concentration of the polymer used, stirring speed, temperature, and preparation method [3]. However, a single design is insufficient to choose the appropriate CPPs and CMAs because various CPPs and CMAs are engaged in the preparation process. The face-centered central composite design (CCD) was used to select CQAs, or solubility, drug loading, and drug release, as dependent variables [4]. In order to provide a comprehensive understanding of formulation development, the research activity detailed in the current studies includes the systematic development of polymeric composites using the principles of QbD.

FH is a calcium channel blocker frequently used in the treatment of hypertension and angina pectoris. Felodipine (BCS Class II) has low water solubility that limits its dissolution and hence lowers its bioavailability when administered orally. In addition, it undergoes significant first-pass metabolism that lowers its bioavailability to about 15%. Improving the solubility of FH is essential for enhancing its dissolution rate and bioavailability, thereby ensuring that an adequate concentration of the drug enters systemic circulation. Techniques like solid dispersion can provide improvement in solubility and, hence, it is an important element that ensures optimum therapeutic effect with reliable and effective treatments from the administration of FH [5]. Hence aim of the present work is to improve the solubility of poor soluble felodipine by solvent evaporation technique using PVP K30 and PEG 6000 employing the quality-by-design approach. PVP K30 was selected as it has the ability to improve solubility through hydrophilic interaction while PEG 6000 was used due to its ability to reduce crystallinity and improve wettability.

MATERIALS AND METHODS

Felodipine hydrochloride (FH) was obtained from Geneka Healthcare, Sidcul, Haridwar. PVP K30 (Merck, Germany) and PEG 6000 (SD Fine, India) K30 were purchased. Other chemicals used in the study were of analytical grade. The present study was done by using double-distilled.

Defining the QTPP and identification of CQAs

The Quality Target Product Profile (QTPP) was developed following the Quality by Design (QbD)-based approach for drug product development to construct the PVP-PEG polymeric composite with

improved patient compliance and to obtain the desired therapeutic response. Critical quality attributes (CQA), including solubility, drug loading, and amount of drug release (table 1), were determined to

achieve QTPP (table I). The created polymeric composite displayed significant drug absorption all along the GI tract through the solubility, drug loading, and amount of drug release.

Table 1: QTPP for developing solid dispersion polymeric composite

QTPP components	Target	Justification(s)
Dosage form type	Powder	Provide flexibility to develop various dosage forms
Drug delivery type	Drug delivery type	To attain the desired therapeutic effect by immediate release of drug.
Route of administration	Oral	Improved patient adherence.
Packaging	Novel drug delivery system	Solid dispersion can be used to develop novel drug delivery system(s).
Drug product quality attributes	Appearance, Solubility, Drug content, Drug release	Quality parameters.

Preparation of drug polymeric composites using experimental design

Polymeric composites of Felodipine Hydrochloride (FH)-loaded PVP-PEG polymeric composite were developed using the process of solvent evaporation. The FH along with excipients, were entirely solubilized in ethanol to get a transparent solution, ensuring a homogeneous mixture at the molecular level. The prepared solution was then subjected to drying to yield a solid product so that the

polymeric matrix contained evenly dispersed drug molecules. For each batch, precise amounts of FH and polymers (PVP-K30 and PEG 6000) were added to ethyl alcohol to form a clear solution. The resulting solution was spread across a tray and subjected to drying in a tray dryer set at 40 °C. Once completely dried, the entire mass was subjected to trituration using a pestle and mortar for 15 min, then passed through the sieved (Sieve No. 60) sieve and stored. Experimental designs for drug-loaded PVP-PEG solid dispersion polymeric complex formation are detailed in table 2 [6].

Table 2: Experimental design for drug-loaded PVP-PEG solid dispersion polymeric complex formation

S. No.	PVP-K30 (g)		PEG 6000	
	Actual (g)	Coded	Actual (g)	Coded
1	3	+1	3	+1
2	2	0	3	+1
3	3	+1	1	-1
4	2	0	2	0
5	2	0	2	0
6	2	0	2	0
7	1	-1	3	+1
8	2	0	2	0
9	2	0	2	0
10	2	0	1	-1
11	1	-1	2	0
12	3	+1	2	0
13	1	-1	1	-1

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Risk assessment studies

The QTPP was outlined to comprehensively define the desired specifications and quality characteristics of the PVP-PEG polymeric composite of felodipine. For this purpose, preliminary risk estimation studies were conducted to delineate the high-risk critical material and process variables affecting the chosen CQAs. An

Ishikawa fishbone was initially constructed to unearth the ostensible cause-effect relationship(s) between all the possible formulation or process parameters and chosen CQAs. Subsequently, each factor affecting the CQAs (mean solubility, drug loading, and drug release) was assigned to different levels of risk, i. e., low, medium, and high, as a part of the risk estimation matrix (REM) exercise (fig. 1 and table 3) [7, 8].

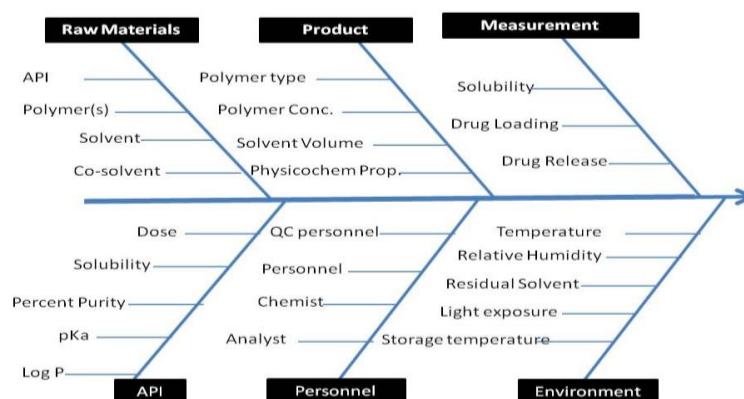


Fig. 3: Ishikawa fishbone diagram depicting critical quality attributes for alginate beads formulation

Table 3: REM for initial risk assessment

Drug product CQA	Melting point	Lipophilicity	Hygroscopicity	Glass forming ability	Polymorphism	Excipients choice	Drug polymer miscibility
Solubility	Low	Medium	Low	Low	High	High	High
Drug Loading	Low	Medium	Low	Low	High	High	High
Drug Release	Low	Medium	Low	Low	High	High	High

Systematic optimization by face centered 3² central composite design (CCD)

For the optimization study, a face-centered 3² CCD was employed. The concentrations of functional Excipients (PVP K30 (X) and PEG 6000 (Y)) were considered as CMA. The impact of the concentration of CMA on CQA i. e. dependent responses, including solubility, drug content, and drug release, was investigated. The design includes the experimental points, as presented in table 3. Polynomial equations were developed to describe the relationship between the independent variables and the responses. The effect of an independent variable can be assessed using the following polynomial equation:

$$Y_1 = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2 + b_6 X_1 X_2^2 + b_7 X_1^2 X_2^2, \text{ eq. (1)}$$

In this equation 1, Y₁ is the dependent response (e. g., solubility, drug content, drug release), X and Y are the independent variables (concentrations of PVP K30 and PEG 6000, respectively), b₀ is the arithmetic mean of the 13 experimental runs, and b₁, b₂, b₃, b₄, and b₅ are the coefficients that represent the linear, quadratic, and interaction effects of the independent variables [9].

The experiments' data were, after that confirmed with a series of statistical parameters to see which model would suit best with experimental data. To see the linkage or association between chosen CMAs and CQAs, response surface methodology was utilized.

Aqueous solubility of FH

Each polymeric composite was prepared by adding an excess amount of powder to 1 ml of distilled water in a 2 ml micro tube, followed by vortexing for sixty seconds. Following this, the microtubes were placed on a mechanical shaker in a water bath (25 °C, 100 rpm) and shaken for 5 days. After shaking, the samples were centrifuged at 5000 g, and 500 µl** of the supernatant was carefully pipetted. The supernatant was then diluted with ethyl alcohol, and the resulting solution was analyzed using a double-beam UV-visible spectrophotometer (UV1800, Shimadzu, Japan) at a wavelength of 363 nm to determine the FH concentration [10].

Drug content (DC) in prepared polymeric composites

For each polymeric composite, a sample equivalent to 5 mg of the drug was weighed and solubilized in a volumetric flask containing ethyl alcohol (100 ml) to prepare a solution of concentration 500 µg/ml. The resulting solution was then filtered through a filter (0.45 µm), and the filtrate was diluted to the appropriate concentration using ethyl alcohol. Analysis of the diluted solution was carried out using a double-beam UV-visible spectrophotometer. (UV1800, Shimadzu, Japan) at a wavelength of 363 nm to determine the concentration of FH. The test was conducted in triplicate for each formulation. The drug content was calculated using the following formula:

$$X_s = X_a/X_t \times 100.$$

Where X_s represents the FH, X_a is the actual titer quantified by the UV-visible spectrophotometer, and X_t is the theoretical concentration [11].

In vitro dissolution (Q)

The dissolution study was conducted using a USP I apparatus (Paddle type, Electrolab dissolution test apparatus, India). A sample equivalent to 5 mg of FH was enclosed within a dialysis membrane, secured in a sinker, and kept in 2% (w/v) aqueous Tween 80 solution (900 ml) for dissolution. The system was maintained at 37±0.5 °C with a water bath surrounding the apparatus. Tween 80 was used for improved dissolution of the drug because of its poor solubility [12]. The speed of the dissolution test apparatus was set to rotate at 100 rpm [13], and the process was done in sink conditions throughout the experiment. Sample (1 ml) was withdrawn at specified time intervals, 1 ml of the

dissolution medium was withdrawn, filtered, and diluted and concentration was analyzed using a UV-visible spectrophotometer (UV1800, Shimadzu, Japan) at 363 nm [14].

Optimization and data validation

Different formulations (table 1) were prepared as per experimental design using the Quality by Design approach employing Design expert Software trial version. A total of 13 batches were prepared among which center point was developed four times to compute the mean for further analysis. The response surface curves (RSM) were plotted using Design Expert® 8.0.7.1 (trial version). The statistical significance of the model was found significant for CQA. After plotting the RSM curve, the optimized batch was selected based on the desired values of the CQA.

The validity of data predicted for the optimized batch was checked by developing four validation check batches (VCB1 to VCB3) as well as the optimized batch was developed and validated. A comparison between observed and predicted values of dependent responses was compared critically. Linear correlation graphs were plotted for the selected validation check batches and residual graphs between predicted and observed responses. The % bias, or percent prediction error, was calculated in relation to the observed responses. Validation of the optimized batch was carried out by selecting four formulations as checkpoints [15].

Powder X-ray diffraction (XRD) analysis

The crystalline characteristics of the FH and optimized polymeric composite were determined using XRD equipment (Philips PW 1729 X-ray diffractometer Le group interconnection, Scient Jurie, Cadlada). XRD study was performed by generating radiation from the monochromatic copper source at 50 kV Voltage and 100 mA current. The PXRD pattern was obtained within a range of 10–70° using a 2θ scan mode, with a scanning speed of 5° per minute and a step size of 0.02° per second [16].

DSC analysis

The crystallinity of the drug and formulation was identified by a Differential Scanning Calorimeter (DSC-60, Shimadzu, Japan). The drug was heated at a rate of 10 °C per minute in the temperature range of 3–400 degrees Celsius under an inert nitrogen atmosphere with a flow rate of 40 ml per minute. A sample weight of 2–3 mg was placed in a sampling pan of aluminum, with an empty pan of aluminum used as the reference. The DSC curves were plotted and analyzed for further study [17].

Scanning electron microscopy

The surface topography of FH plain powder and the optimized polymeric composite was observed using a Scanning Electron Microscope (Zeiss, Supra 40, India). The sample was fixed on a brass disc support using thin carbon tape. In order to render the samples electrically conductive for imaging, they were coated with platinum using an EMI Teck Ion Sputter (K575K) for three minutes at a vacuum of 8×10–3 mbar, with a current of 20 mA and 90% turbo speed [18].

RESULTS AND DISCUSSION

Even though FH is poorly soluble in aqueous gastrointestinal fluids, its own absorption is restricted. Solid dispersion techniques are known to increase the water solubility, rate of drug dissolution, and absorption of rugs having poor solubility [19]. Both PVP and PEG were incorporated into all batches to improve the water solubility of FH [20]. In this study, to prepare a hydrophilic polymeric composite, PVP K-30 and PEG 6000 were used as hydrophilic polymers and polymeric surfactants, respectively.

Risk estimation matrix

An Ishikawa fishbone diagram, illustrated in fig. 3, schematically represents all possible connections between the different input variables and the intended CQAs of polymeric composites. By taking previously published findings and brainstorming sessions into consideration, the criticality of some input variables was reviewed; every one of these variables harbored a varying degree of risk. All other input variables were kept constant in the experiment except CMA which includes PVP-K30 concentration, PEG 6000, stirring speed, solvent volume, and stirring time were considered to be risk factors; thus, tests of factor screening were taken into consideration [21].

Factor screening studies

Factor screening studies are known to follow the sparsity effect, i. e., "only a vital few" out of so many possible variables tend to explain the leading cause of the variation during the experimentation.

Below mentioned equations 1. 2 and 3 define the coefficients of different quadratic model terms involved during the analysis of individual CQAs.

$$\text{Solubility} = +23.03 + 4.46A + 3.98B - 0.59AB + 0.44A^2 + 0.20B^2 + 0.18A^2B + 0.40AB^2 - 0.13A^2B^2 \dots \text{Eq (1)}$$

$$\text{Drug content} = +97.36 + 0.41A - 1.94B + 0.070AB + 0.12A^2 + 0.19B^2 + 0.095A^2B + 0.06AB^2 - 0.085A^2B^2 \dots \text{Eq (2)}$$

$$\text{Drug Release} = +80.41 + 4.40A + 2.90B - 0.31AB + 0.12A^2 + 0.90B^2 - 0.55A^2B - 0.55AB^2 - 0.27A^2B^2 \dots \text{Eq (3)}$$

Where A indicates the concentration of gelatin and B represents the concentration of the linear was found highly significant ($p < 0.0001$) for all three dependent variables and provides the best fit. The calculated R^2 value in the present models for all four responses was close to 1 indicating a good model. In all cases, the adjusted R^2 values are in reasonable agreement with the predicted R^2 values (0.09877 and 0.9748 for solubility, 0.9800 and 0.9764 for drug content, and 0.9701 and 0.9521 for drug release. "Adeq Precision" measures the signal-to-noise ratio and a ratio greater than 4 was desirable. In all the cases precision values for four responses were found to be 17.264, 24.474, and 48.163 indicating an adequate signal and that the model can be used to navigate within the design space.

The solvent-evaporation method was chosen for the preparation of the solid dispersions, as it is considered one of the most effective techniques. In this approach, before drying, each component is thoroughly dissolved in a solvent to ensure uniform molecular mixing. Consequently, the dried product's drug molecules are evenly dispersed or trapped within the polymeric matrix, enhancing content homogeneity and encouraging improved drug-hydrophilic polymeric matrix interaction. This leads to enhanced solubility and dissolution proliferation of the drug, as the hydrophilic polymers aid in better wetting of the drug. Drying was carried out at 40 °C until the sample weight stayed constant in order to ensure that the solvent was completely removed [22].

Table 4: Characterization of developed solid dispersion complex

S. No.	PVP-K30 (g)	PEG 6000 (g)	Solubility (mg/ml) (n=3, Mean±SD)	Drug content (%) (n=3, Mean±SD)	Drug release (%) (n=3, Mean±SD)
SD1	1	1	31.98±0.19	96.28±1.02	87.05±0.88
SD2	0	1	27.21±1.71	95.61±0.91	84.21±0.43
SD3	1	-1	24.83±0.64	99.82±1.33	82.97±0.45
SD4	0	0	23.01±0.41	97.47±.75	80.83±1.06
SD5	0	0	22.91±0.09	97.52±0.19	80.56±1.08
SD6	0	0	23.23±0.37	97.43±0.73	80.72±0.79
SD7	-1	1	23.44±0.38	95.19±1.05	79.97±0.52
SD8	0	0	22.89±0.82	97.74±1.27	80.00±0.93
SD9	0	0	23.07±0.55	97.00±0.79	80.18±1.01
SD10	0	-1	19.25±0.71	99.48±0.37	78.41±0.49
SD11	-1	0	19.02±0.63	97.06±1.05	76.13±0.84
SD12	1	0	27.93±0.39	97.89±1.17	84.93±0.39
SD13	-1	-1	13.93±0.44	99.01±0.98	74.66±1.09

*n=3 for all experiments, indicating the number of replicates, *Data are presented as mean±SD (Standard Deviation).

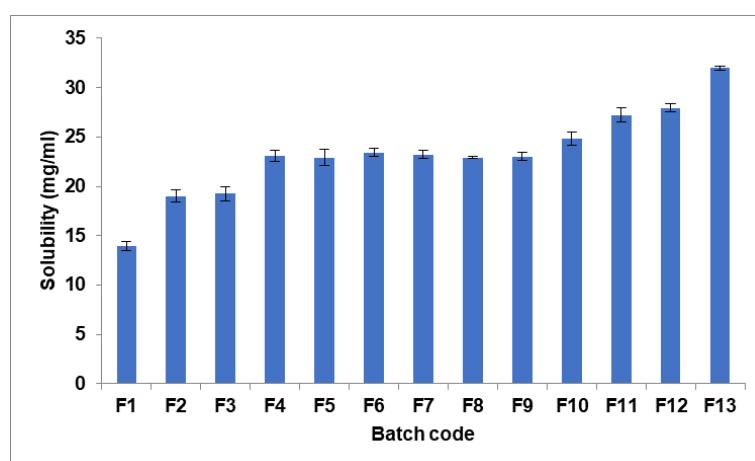


Fig. 2: Solubility study of various PVP-PEG solid dispersion polymeric composites (Data are expressed as mean±standard deviation (SD), with error bars representing SD, n = 3)

Solubility study

All of the prepared polymeric composites show a positive impact over solubility (table 4 and fig. 2). In solid dispersion systems, PVP

K30 acts as a hydrophilic polymer that facilitates the solubilization of poorly soluble drugs by increasing their wettability and dispersibility in aqueous media. PEG 6000, on the other hand, is a hydrophilic polymeric surfactant that enhances the dissolution rate

by reducing the crystalline structure of the drug and promoting its amorphization [23].

When PVP K30 and PEG 6000 were combined in a polymeric composite solid dispersion formulation, a synergistic effect is observed, leading to a significant improvement in the solubility of the drug. PVP K30 helps in maintaining the drug in a molecularly dispersed form, preventing recrystallization, while PEG 6000 contributes to further enhancing the solubility through its surfactant properties. This combination increases the available surface area for dissolution and improves the interaction between the drug molecules and the solvent, resulting in faster dissolution and higher solubility [24].

The t-test analysis demonstrated that both PVP K30 and PEG 6000 significantly influence solubility, drug content, and drug release. PVP K30 showed a strong impact on solubility ($p = 0.0367$) and drug release ($p = 0.0119$), likely due to its ability to form hydrogen bonds and improve drug dispersion in an amorphous state, enhancing dissolution. Similarly, PEG 6000 exhibited a significant effect on drug content ($p = 0.0001$) and also contributed to solubility and drug release, possibly by reducing drug crystallinity and enhancing wettability. The combined effects of PVP K30 and PEG 6000 suggest a synergistic role in improving solubility, maintaining uniform drug content, and facilitating better drug release. Optimizing the concentrations of both polymers is crucial for enhancing the overall performance of solid dispersions.

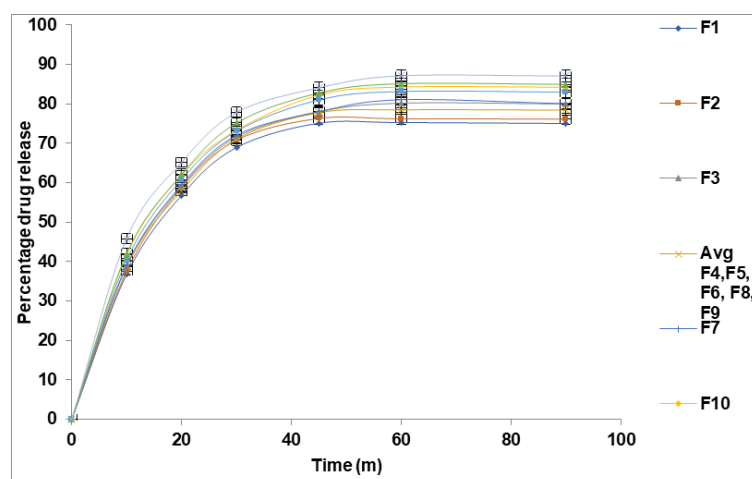


Fig. 3: Drug release profile of formulations F1–F13 over time. (Data are expressed as mean±standard deviation (SD), with error bars representing SD, n = 3)

Drug content determination

Before conducting the drug dissolution study, the drug content was assessed all batches. Table 4 displays the drug content for all formulations, indicating that the drug remained steady throughout the formulation development and procedures for drying. The combination of PVP K30 and PEG 6000 in solid dispersions enhances drug content uniformity and solubility. PVP K30 increases drug wettability and dispersion, while PEG 6000 reduces crystallinity, promoting amorphization and faster dissolution. Together, they improve drug stability, ensure better distribution, and enhance bioavailability, making the formulation more effective [25].

In vitro drug release study

The drug release study developed a solid dispersion polymeric composite shown in table 4 and fig. 3. All prepared polymeric composites were evaluated for their drug release over a period of 8 h. The Study reveals that the increased drug release rate of the formulations due to differences in the concentrations of the dependent variables. Specifically, as the amount of PVP K30 increased from 1g to 3 g, the drug release rate increased. This enhances the wettability and drug dissolution in aqueous media, thus improving its release rate [26].

Data analysis

Data obtained from the study clearly indicate that the solubility, drug content, and drug release values are strongly dependent upon the selected independent variables (equations 2-4) The ANOVA results for the different dependent variables are as follows:

$$SOL = 23.03 + 4.46A + 3.98B - 0.59AB + 0.44A^2 + 0.20B^2 + 0.18A^2B + 0.40AB^2 - 0.13A^2B^2 \text{ eqn 2}$$

$$DC = 97.36 + 0.41A - 1.94B + 0.070AB + 0.12A^2 + 0.19B^2 + 0.095A^2B + 0.06AB^2 - 0.085A^2B^2 \text{ eqn 3}$$

$$Q = +80.41 + 4.40A + 2.90B - 0.31AB + 0.12A^2 + 0.90B^2 - 0.55A^2B - 0.27A^2B^2 \text{ eqn 4}$$

Where A indicates the concentration of PVP K30 and B represents the concentration of PEG.

Drug release kinetics

The dissolution kinetic study revealed that the Korsmeyer-Peppas model best described the drug release behavior for all formulations, indicating a non-Fickian diffusion mechanism governed by both diffusion and erosion processes. The release rate constant (k value) ranged from 25.05 to 29.95, while the diffusional exponent (n value) between 0.25 and 0.28 confirmed anomalous transport. Higher drug release was observed in F10 to F13, suggesting that polymer composition and excipient selection significantly influence the release profile. These findings emphasize the need for optimized formulation strategies to achieve desired drug release characteristics.

Response surface analysis

To examine response properties, response surface plots and contour plots were prepared as displayed in fig. 4 (a) for solubility, (b) for drug content, and (c) for drug release.

The concentration of independent variables was established (see table 4). Thirteen formulations were created by selecting various combinations, with the center point replicated five times to determine a mean value for further analysis. The effects of these independent variables were evaluated using statistical software (Design Expert, trial version DX10). A model was developed and tested for significance to optimize the batch using response surface methodology. Data optimization was further confirmed by generating an overlay plot with Design Expert software. Validation of the optimized batch involved creating four validation check batches (VC1-VC3), and the dependent responses (solubility, drug content, and drug release) were measured. These observed values were then compared to the predicted responses, and the percent error was calculated.

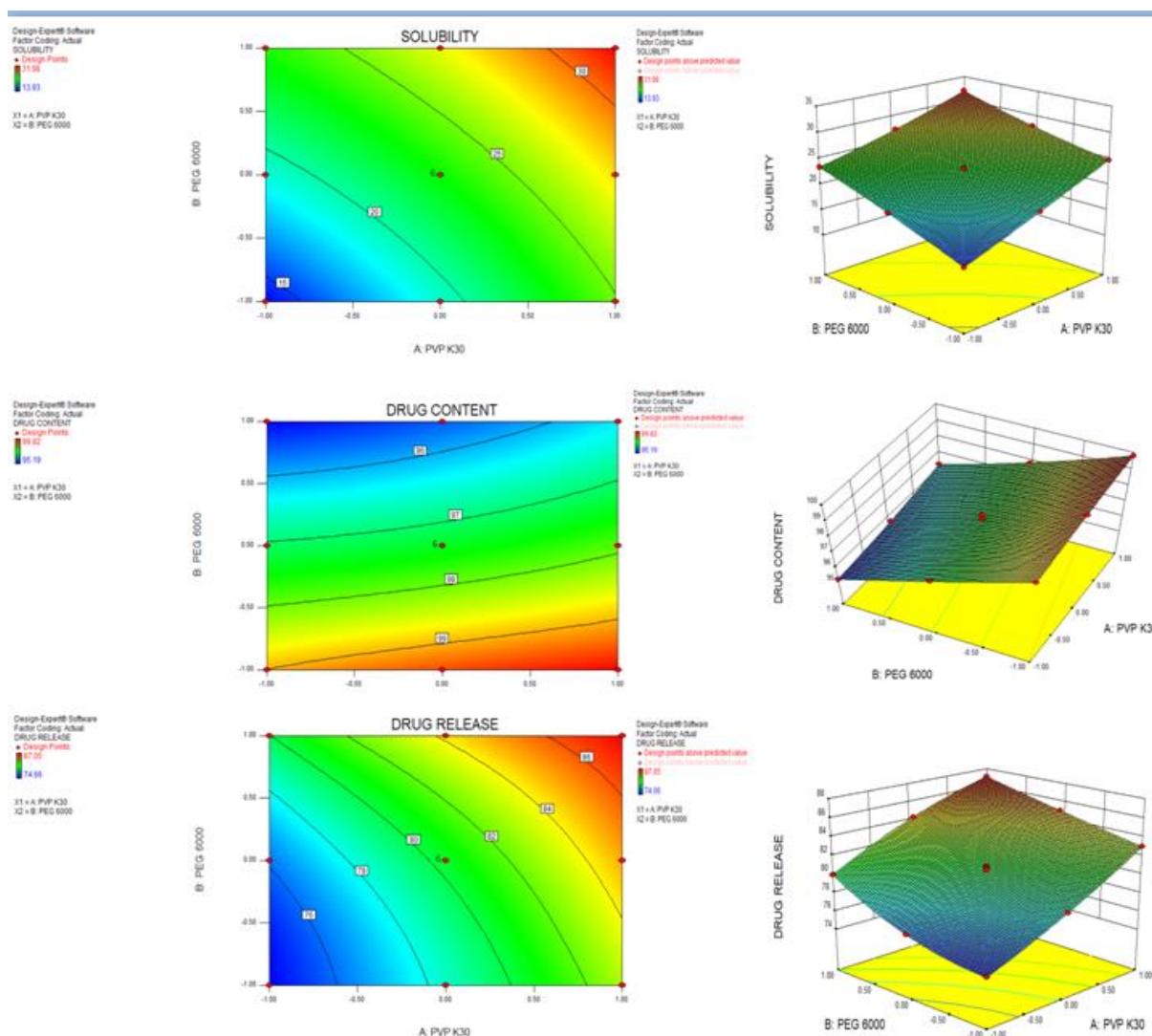


Fig. 4: Response surface and contour plots for (a) Solubility (b) Drug content and (c) Drug release

Response surface curve (fig. 4a) clearly indicates the impact of PVP K30 over solubility of developed solid dispersion complex that as the concentration of PVP K30 increases solubility increases by altering its crystalline structure to a more amorphous form, which dissolves more readily in the water while as the concentration of PEG 6000 increases solubility also get increases by increasing the overall surface area available for dissolution.

Response surface curve (fig. 4b) shows that as the amount of PVP K30 increases drug content also improves as PVP K30 can help to amorphized drugs that are typically crystalline and poorly soluble in water while by increasing the concentration of PEG 6000 drug content increases.

The response surface curve (fig. 4c) of the drug release study shows that as the concentration of PVP K30 increases drug release increases while as the increase in concentration of PEG 6000 also result into improved drug release from the solid dispersion.

Overlay plot

The overlay plot in fig. 5 reveals significant interactions between PVP K30 and PEG 6000 in affecting the responses. For example, the highest solubility and drug release are typically observed in regions where both polymers are present in higher concentrations, indicating synergistic effects. However, at higher concentrations of

PEG 6000, the drug content starts to plateau or decrease, suggesting that there is an optimal balance between the two polymers.

As seen in the plot, there are some trade-offs. For instance, drug release and solubility are maximized with higher levels of both PVP K30 and PEG 6000, but this comes at the cost of drug content, which may decrease when the polymer levels become too high. The overlay plot helps in identifying the regions where an optimal balance can be achieved to maximize solubility and release, while still maintaining a sufficient drug content.

Validation of the statistical model

The predicted responses for all the formulated batches and their corresponding experimentally observed values were found to be in close agreement, as shown in table 5 and fig. 6. This indicates that the models developed to predict the responses were not only statistically significant but also valid, as they yielded values that closely matched the experimentally observed results. The overlay plot shows the trade-offs between drug release, solubility, and drug content based on PVP K30 and PEG 6000 concentrations. The yellow region represents the optimized formulation where all parameters meet the desired limits. Higher PVP K30 enhances solubility but may affect drug release, while PEG 6000 improves drug release but may impact solubility. Balancing these factors is crucial for an optimal formulation.

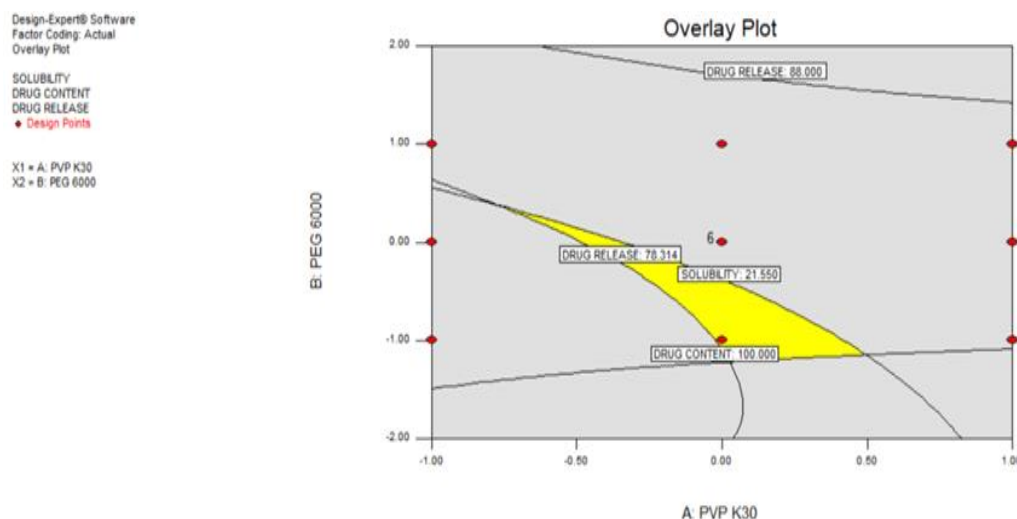


Fig. 5: Overlay plot indicating interactions between independent variables

Table 5: Validation checkpoint compositions and their results

Formulation code	X1	X2	Response	Predicted value (n=3, mean±SD)	Actual value (n=3, mean±SD)	% Error
Optimized batch	0.02	-1.16	Solubility	18.8±0.36	18.75±0.13	0.0027
			Drug Content	99.87±1.19	99.79±0.88	0.0008
			Drug release	78.34±1.47	78.28±0.73	0.0008
VC1	-0.68	0.29	Solubility	21.49±0.09	21.53±0.17	-0.0019
			Drug Content	96.57±1.31	96.52±1.11	0.0005
			Drug release	78.4±1.20	78.33±1.06	0.0009
VC2	0.44	-1.09	Solubility	21.43±0.37	21.19±0.21	0.0112
			Drug Content	99.84±1.06	99.58±0.83	0.0026
			Drug release	80.21±1.28	80.17±0.98	0.0005
VC3	0.03	-0.48	Solubility	21.33±0.33	21.2±0.61	0.0061
			Drug Content	98.34±0.97	98.04±1.31	0.0031
			Drug release	79.38±0.61	79.29±1.19	0.0011

*n=3 for all experiments, indicating the number of replicates, *Data are presented as mean±SD).

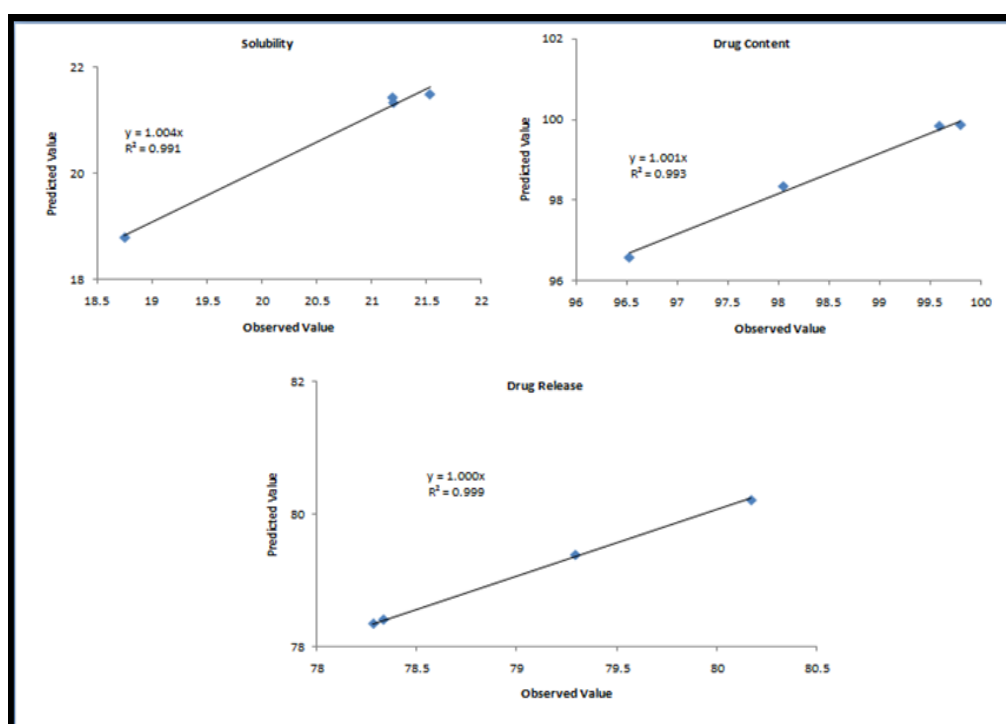


Fig. 6: Regression coefficient between predicted and experimental response(a) Solubility (b) Drug content (c) Drug release

The Fourier Transform Infrared (FTIR) analysis of the developed solid dispersion complex was conducted to observe the potential interactions between the drug and the polymer used in their formulation. FTIR spectra of pure drug FH (fig. 8) show characteristic absorption peaks at (3335.02 cm⁻¹ is due to N-H stretching, 3026.95 cm⁻¹ is due to stretching of the C-H bond, the peaks at 1651.09 cm⁻¹ is due to C=O bonds (carbonyl group), peak at 1591.98, 1490.38 and 1467.67 cm⁻¹ are due to C=C bond of benzene ring, 1382.81 cm⁻¹ is due to C-N stretching, 1035.32 cm⁻¹ is due to C-O-C stretching of ester, 824.05, 761.20 cm⁻¹ are due to

substituted benzene ring and 592.35 cm⁻¹ is due to Cl stretching). The analysis revealed that the infrared spectra of the pure drug and the developed solid dispersion exhibit similar peak patterns (as shown in table 4 and fig. 7). This observation suggests that there is a lack of significant interaction between the drug and the polymer during the formulation process. The consistent peak alignment indicates that the drug's molecular integrity is maintained within the microspheres, reinforcing the compatibility of the selected polymer with the active ingredient. Observations indicated that there is no change in the fundamental properties of the drug.

Table 6: IR interpretation of solid dispersion

IR frequencies (cm ⁻¹)	Assignments
3335.02	N-H stretching
3026.95	C-H bond
1651.09	C=O bonds (carbonyl group)
1591.98, 1499.38 and 1467.67	C=C bond
1382.81	C-N stretching
1035.32	C-O-C stretching of ester,
824.05, 761.20	substituted benzene ring
592.35	Cl stretching

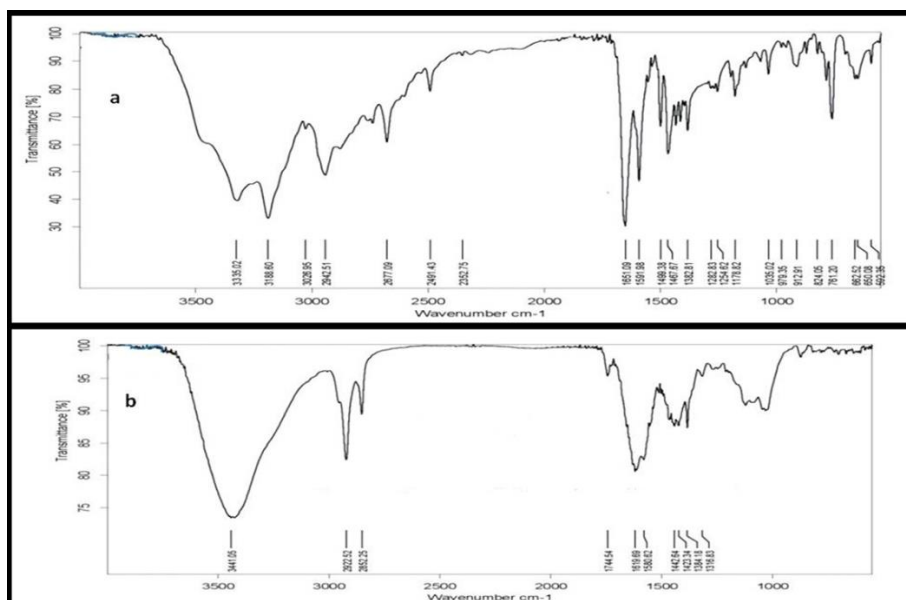


Fig. 7: FTIR spectra of (a) Pure drug and (b) optimized solid dispersion

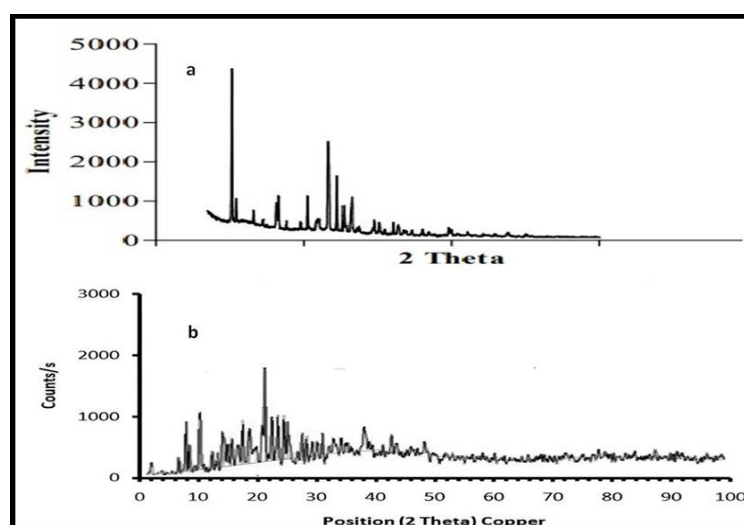


Fig. 8: XRD pattern of (a) pure drug and (b) Optimized batch of FH

Crystalline property

XRD and DSC were used to examine the sample's crystalline characteristics. Results are shown in fig. 9. The XRD analysis of the powdered drug showed sharp, intense peaks. This indicates it has some crystalline characteristics. However, the drug-loaded PVP-PEG solid dispersion complex (fig. 9) showed no peaks. This indicates a transition to an amorphous state. The loss of crystallinity in the solid dispersion of felodipine enhances its solubility and dissolution rate by reducing lattice energy and increasing molecular mobility. The polymer matrix further

improves wettability and prevents recrystallization, leading to better drug release and bioavailability [27].

Surface morphology

The surface topography of pure drug and drug-loaded solid dispersion formulation are shown in fig. 9. The SEM of pure drug shows irregular shape as well as external surface structure while the drug-loaded particles were prepared by solid dispersion polymeric composites were found of irregular shape and surface [28].

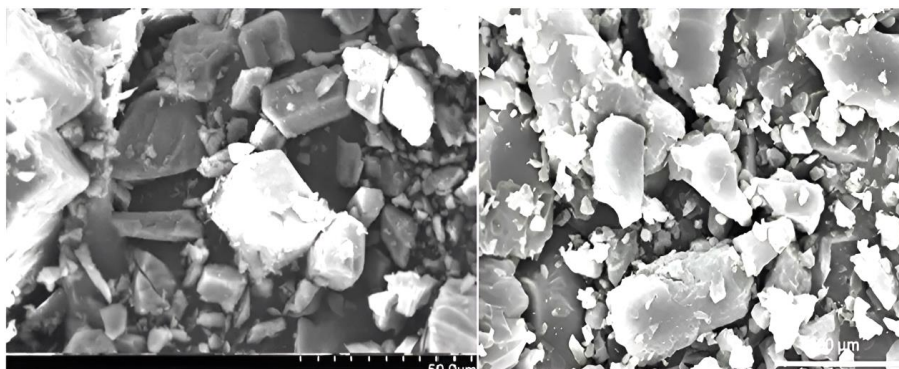


Fig. 9: Scanning electron microscope for (a) FH pure drug and (b) optimized solid dispersion complex

Stability study of the optimized formulation

A stability study of optimized formulation was conducted for three months in the stability study chamber under accelerated conditions

as per ICH guidelines (temp. 40 ± 2 °C and RH $75 \pm 5\%$). It was observed that over this period of time, dependent responses like solubility, drug content, and drug release were found within permissible limits [29].

Table 7: Stability study of the optimized formulation

Formulation code	Response	After 15 d (60 °C)	After 3 mo (40 °C and RH 75)
Optimized batch	Solubility (mg/ml) (n=3, Mean \pm SD)	18.8 \pm 0.36	18.35 \pm 0.13
	Drug Content (%) (n=3, Mean \pm SD)	99.87 \pm 1.19	99.08 \pm 0.88
	Drug release (%) (n=3, Mean \pm SD)	78.34 \pm 1.47	77.73 \pm 0.73

*n=3f rallex periments, indicating the number frepicates, *Data are presented as mean \pm SD

CONCLUSION

In conclusion, the study successfully developed a polymeric composite of felodipine using a Quality by Design (QbD) approach to enhance its solubility and bioavailability. The QTTP was achieved by identifying key CQAs, including drug solubility, drug content, and drug release. Additionally, risk assessment studies were conducted to determine the critical material attributes (CMAs) and critical process parameters (CPPs) that could influence the CQAs of the formulated beads. The use of PVP-K 30 and PEG 600 as CMA in varying concentrations effectively improved the CQAs as the drug's solubility, drug content, and drug release. The optimization process, guided by response surface methodology, demonstrated accurate predictions and successful validation of the composite formulation. The findings confirm the potential of this approach in improving the solubility of poorly soluble drugs, offering a promising strategy for enhancing their bioavailability in therapeutic applications.

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AUTHORS CONTRIBUTIONS

Deepti Agarwal carried out experiments in this research. Dr. Vijay Sharma and Dr. R. D. Gupta contributed to writing, experimentation, data analysis, result reporting, and original draft preparation.

CONFLICT OF INTERESTS

The authors do not have any conflict of interest.

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